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MORPHOLOGIC STUDIES

# Status of the Myocardium and Infarct-Related Coronary Artery in 19 Necropsy Patients With Acute Recanalization Using Pharmacologic (Streptokinase, r-Tissue Plasminogen Activator), Mechanical (Percutaneous Transluminal Coronary Angioplasty) or Combined Types of Reperfusion Therapy

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**In acute myocardial infarction, myocardial salvage is dependent on rapid restoration of blood flow. Pharmacologic (streptokinase, recombinant tissue-type plasminogen activator), mechanical (percutaneous transluminal coronary angioplasty, guide wire perforation) or combined forms of reperfusion therapy can accomplish this goal, but their effects on infarcted myocardium and vessel occlusion site have not been compared at necropsy. The heart of 19 necropsy patients who had received various forms of acute reperfusion therapy was studied: 14 had pharmacologic or combined forms of reperfusion therapy (13 streptokinase and 1 tissue-type plasminogen activator, including 4 with combined balloon angioplasty) and 5 had had purely mechanical (balloon angioplasty) reperfusion therapy. Reperfusion was initially clinically successful in all 19 patients with the average time from onset of symptoms to reperfusion being 3.7 hours.**

**Necropsy observations separated the 19 patients into distinct subgroups based on changes in the myocardium and infarct-related coronary arteries. Of the 19 patients, 14 (74%) had hemorrhagic myocardial infarction and they all received pharmacologic or combined forms of reperfusion therapy. The remaining five patients (26%) had nonhemorrhagic (anemic) infarction and were treated with balloon angioplasty therapy alone. Increased luminal cross-sectional area was present in 8 of 9 patients with acute balloon angioplasty but severe coronary atherosclerotic plaque remained in 9 of 10 patients without acute balloon angioplasty. Severe hemorrhage surrounded angioplasty sites in all four patients who also received streptokinase or tissue-type plasminogen activator. Severe bleeding at the angioplasty site compromised the dilated coronary lumen in one patient. No patient with angioplasty alone had intraplaque bleeding.**

**Thus, acute coronary balloon angioplasty reperfusion therapy alone appears to avoid the potentially adverse effects of myocardial and intraplaque hemorrhage while simultaneously increasing luminal cross-sectional area at the site of acute occlusion.**

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The focus of management and treatment of patients with evolving acute myocardial infarction is currently directed toward limiting the amount of myocardial necrosis. Nonsurgical attempts to salvage jeopardized myocardium have employed methods of rapid restoration of coronary blood flow using *purely pharmacologic* (streptokinase, urokinase, tissue-type plasminogen activator), *purely mechanical* (percutaneous transluminal balloon angioplasty, guide wire perforation) or *combined* types of reperfusion therapy. Despite the widespread use of various forms of reperfusion therapy,

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**Table 1.** Certain Clinical and Morphologic Observations in 19 Necropsy Patients With Acute Myocardial Infarction Undergoing Various Types (mechanical, pharmacologic, combination) of Reperfusion Therapy

| | Thrombolytic Therapy With (+) or Without (−) PTCA | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Streptokinase Only (n = 9) | | | | | | | | |
| Clinical data | | | | | | | | | |
| 1. Age (yr) & Sex | 46M | 51M | 55M | 58M | 60M | 63M | 66M | 66M | 66F |
| 2. Location AMI | P | A | A | A | P | A | A | P | A |
| 3. Infarct vessel | LC | LAD | LAD | LAD | R | LAD | LAD | R | LAD |
| 4. Form of reperfusion therapy | | | | | | | | | |
| a) Mechanical | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| b) Pharmacologic (dose) (units) | IV 2.7 million | IC 160,000 | IC 200,000 | IC 250,000 | IC 275,000 | IC 195,000 | IC 175,000 | IV 1.5 million | IV 900,000 |
| 5. Interval onset symptoms to reperfusion (hours) | 3.5 | 4.0 | 3.5 | 4.5 | 4.0 | 3.0 | 2.5 | 3.5 | <4 |
| 6. Initially angiographically successful reperfusion | —[h] | + | + | + | +[a] | + | + | —[b] | + |
| 7. Interval reperfusion to death (hours) | — | 72 | 24 | 24 | 16 | 96 | 48 | 72 | — |
| 8. Interval onset of symptoms to death (days) | 3.8 | 3.2 | 1.2 | 1.2 | 0.9 | 4.1 | 2.1 | 3.1 | 4.0 |
| 9. Mode of death | PCHF | PCHF | PCHF | PCHF | PCHF | PCHF | PCHF | SVF | M Rup |
| Necropsy data | | | | | | | | | |
| 1. Type transmural AMI | | | | | | | | | |
| a) Anemic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| b) Hemorrhagic | + | + | + | + | + | + | + | +[c] | + |
| 2. Histology of AMI | | | | | | | | | |
| a) Contraction band necrosis | + | + | + | + | + | + | + | +[c] | + |
| b) Coagulation necrosis | + | + | + | + | + | + | + | + | + |
| c) Interstitial necrosis | + | + | + | + | + | + | + | 0 | + |
| d) Interstitial extravasated RBC (0 to 4) | 4+ | 4+ | 4+ | 4+ | 4+ | 4+ | 4+ | 1+ | 4+ |
| 1) Massive (grossly visible) | + | + | + | + | + | + | + | 0 | + |
| 2) Focal (microscopic only) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 |
| 3) Extravasated RBC limited to necrotic zone | + | 0 | 0 | + | + | 0 | + | + | + |
| 3. Histology of infarct coronary artery | | | | | | | | | |
| a) Residual thrombus | + | + | + | + | + | + | + | + | 0 |
| 1) Occlusive | + | 0 | 0 | 0 | + | + | + | + | 0 |
| b) Underlying atherosclerotic plaque (% XSA) | 51 to 75 | >75 | >75 | >75 | >75 | >75 | >75 | >75 | >75 |
| c) Intraplaque hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| d) Intimal-medial "crack" | +[h] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[a]Initial reperfusion but subsequent thrombosis; [b]coronary angiogram not performed but slight decrease in chest pain initially after streptokinase therapy; [c]minute trace of myocardial hemorrhage indicating temporary or partial reperfusion; [d]unable to significantly open left main artery with infusion of streptokinase or attempt at guide wire perforation; [e]focal areas of mild fiber hypereosinophilia; [f]coronary artery dissection with adventitial hemorrhage; [g]initial flap with surrounding thrombus; [h]streptokinase one day before unsuccessful angioplasty.

A = anterior (anteroseptal); AMI = acute myocardial infarction; CA Rup = coronary artery rupture; F = female; Fo = focal; GWP = guide wire

few necropsy observations have been reported describing resultant changes in myocardium or infarct-related coronary arteries (1–14). Thus far, necropsy observations have been limited to patients receiving either streptokinase (1–10,12,14) or urokinase (11,13) thrombolytic therapy. This report of 19 necropsy patients with evolving acute myocardial infarction compares the status of ventricular myocardium and infarct-related coronary artery in patients undergoing purely pharmacologic (streptokinase or tissue-type plasminogen activator), purely mechanical (percutaneous transluminal coronary angioplasty) or combined forms of acute reperfusion therapy.

## Methods

**Clinical and morphologic definitions.** *Time from onset of symptoms to reperfusion.* This was defined as the interval from the onset of clinical symptoms to angiographic visualization of the distal coronary artery segment in the totally occluded infarct artery. In three patients, intravenous strep-

**Table 1.** (*continued*)

| Thrombolytic Therapy With (+) or Without (−) PTCA | | | | | Percutaneous Transluminal Coronary Angioplasty Only (n = 5) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PTCA + S (n = 3) | | | S + Guide Wire (n = 1) | r-TPA + PTCA (n = 1) | | | | | |
| 52M | 54M | 58M | 44F | 45F | 52M | 52M | 62M | 63M | 66M |
| A | A | A | A | A | A | P | A | A | P |
| LAD | LAD | LAD | LM | LAD | LAD | R | LAD | LAD | R |
| + | + | + | GWP | + | + | + | + | + | + |
| IC | IC | IC | IC | IC | 0 | 0 | 0 | 0 | 0 |
| 50,000 | 80,000 | 70,000 | 80,000 | 80 mg | | | | | |
| 4.0 | 3.5 | 4.5 | 3.5 | 3.5 | 3.5 | 4.0 | 4.5 | 4.0 | 3.0 |
| +[a] | + | + | +[d] | + | + | + | + | + | + |
| — | 44.5 | 16 | — | 12 | 20.5 | 44 | 259.5 | 2 | — |
| 1.0 | 2 | 0.9 | 1 | 0.6 | 1 | 2 | 11 | 0.3 | 11 |
| PCHF | VF | PCHF | PCHF | CA Rup | VF | VF | NC | SVF | M Rup |
| 0 | 0 | 0 | 0 | 0 | + | + | + | + | + |
| + | + | + | + | + | 0 | 0 | 0 | 0 | 0 |
| + | + | + | + | +[Fo] | + | + | + | +[Fo] | + |
| + | + | + | + | + | + | + | +[Fo] | 0[e] | + |
| + | + | + | + | + | +[Fo] | +[Fo] | +[Fo] | 0 | + |
| 4+ | 4+ | 4+ | 4+ | 4+ | 1+ | 1/2+ | 0 | 0 | 1+ |
| + | + | + | + | + | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | + | + | 0 | 0 | + |
| + | + | + | 0 | + | + | + | − | − | + |
| + | + | + | + | 0 | + | + | 0 | + | + |
| 0 | 0 | + | 0 | 0 | + | + | 0 | 0 | + |
| >75 | 51 to 75 | 51 to 75 | >75 | 51 to 75 | 51–75 | 51–75 | 51–75 | 51–75 | 51–75[g] |
| + | + | + | 0 | + | 0 | 0 | 0 | 0 | 0 |
| + | + | + | 0 | +[f] | + | + | + | + | + |

perforation; IC = intracoronary; IV = intravenous; LAD = left anterior descending artery; LC = left circumflex coronary artery; LM = left main artery; M = male; M Rup = myocardial rupture; NC = noncardiac; P = posterior ("inferior, inferoseptal, posteroseptal"); PCHF = progressive congestive heart failure; PTCA = percutaneous transluminal coronary angioplasty; R = right; r-TPA = recombinant tissue-type plasminogen activator; S = streptokinase; SVF = sudden unexpected ventricular fibrillation; XSA = cross-sectional area; VF = ventricular fibrillation; + = positive or present; 0 = negative or absent; — = no data or not applicable.

tokinase therapy was given without initial coronary angiographic monitoring and an estimate of reperfusion time was assessed by lessening of symptoms and pertinent electrocardiographic findings (reperfusion ventricular arrhythmia and reduction of ST segment elevation) after administration of streptokinase.

*Angiographically successful coronary reperfusion.* Initially successful coronary reperfusion was defined as visualization of the distal coronary artery segment in the totally occluded infarct artery. In patients without coronary angiography, this determination was not possible.

*Progressive congestive heart failure.* The mode of death in 10 patients was progressive signs and symptoms of congestive heart failure (pulmonary edema) due to underlying acute myocardial infarction.

*Location of acute myocardial infarction.* The infarct site was classified anatomically as anterior or posterior. Anterior infarcts included myocardial necrosis of the anterior left ventricular free wall with or without associated involvement of ventricular septum or lateral free wall. Posterior infarcts included myocardial necrosis of the posterior left ventricular free wall ("inferior" infarct) with or without associated

involvement of ventricular septum or lateral free wall. All infarcts were *transmural* (defined as involvement of greater than the inner one-half of the left ventricular wall).

*Infarct vessel.* The major epicardial coronary artery corresponding to the zone of infarction was termed the *infarct-related artery.*

*Interstitial extravasated erythrocytes.* The presence of extravasated erythrocytes within the myocardial interstitial space was classified as *massive* extravasation (grossly and microscopically visible) or *focal* extravasation (microscopically visible only). The presence of massively extravasated erythrocytes producing grossly visible myocardial hemorrhage was termed *hemorrhagic infarction.* In contrast, focal areas of interstitial erythrocytes apparent only on microscopic examination did not produce grossly visible myocardial hemorrhage and were classified under *anemic infarction* with interstitial extravasated erythrocytes. The degree of interstitial extravasated erythrocytes was graded as mild and focal (1+), mild and extensive (2+), moderate and extensive (3+) or severe and extensive with sheets of packed erythrocytes (4+).

*Residual coronary artery thrombus.* A grossly or histologically detectable collection of fibrin, platelets and erythrocytes along the coronary artery wall was defined as residual thrombus. Thrombus filling the residual coronary artery lumen was defined as *occlusive* thrombus.

**Patients studied.** Between September 1982 and June 1986, the heart from 19 necropsy patients who had received various forms of reperfusion therapy for evolving acute myocardial infarction was examined. The hearts were obtained from four hospitals in two states. Gross and histologic examinations were evaluated independently by the local hospital pathologists and all hearts were examined grossly and histologically by one of us (B.F.W.). Medical records including results of cardiac catheterization and coronary angiography were reviewed for each patient.

Table 1 summarizes certain clinical information in the 19 necropsy patients receiving reperfusion therapy for evolving acute myocardial infarction. Age at death ranged from 44 to 66 years (average 57), and 16 (85%) of the patients were men. The acute myocardial infarct was located anteriorly in 14 patients (74%) and posteriorly in 5 (26%). No patient had clinical evidence of infarct extension or reinfarction after reperfusion therapy. The infarct-related artery was the left anterior descending coronary artery in 13 anterior infarcts, the left main coronary artery in 1 anterior infarct, and the right (4 infarcts) or left circumflex (1 infarct) coronary artery in the remaining 5 posterior infarcts. Of the 19 patients, 16 had an angiographically documented *totally occluded infarct-related coronary artery* before onset of reperfusion therapy. The remaining three patients had intravenous streptokinase therapy without preceding coronary angiography.

**Pathologic studies.** At least eight histologic sections stained with hematoxylin-eosin (each myocardial sample measuring about 2.5 × 1.5 cm) were obtained from the left ventricle of each heart (Fig. 1): two sections from the central zone of necrosis, four sections from the transitional zones of infarcted and noninfarcted muscle and two sections from noninfarcted, nontransitional zone myocardium. Each section was evaluated for contraction band and coagulative necrosis and interstitial extravasated erythrocytes. The highest grade (0 to 4+) of extravasated interstitial erythrocytes was recorded. In addition, the infarct-related coronary artery was cut into serial cross sections and stained with hematoxylin-eosin and elastic stains. The amount of luminal cross-sectional area reduction by atherosclerotic plaque or thrombus, or both, was determined by microscopic examination magnified 25 to 50 times. The accuracy of these determinations was verified by videoplanimetry.

## Results

**Clinical data (Table 1).** The acute reperfusion therapy included purely pharmacologic therapy (streptokinase in nine patients), purely mechanical therapy (coronary angioplasty in five patients) and combined forms of reperfusion therapy (coronary angioplasty plus streptokinase in three patients, streptokinase plus guide wire perforation in one patient and recombinant tissue-type plasminogen activator plus coronary angioplasty in one patient).

Patients who received combined forms of reperfusion therapy (angioplasty plus lytic agent) had an acute angioplasty procedure initially followed within minutes by intracoronary streptokinase or tissue-type plasminogen activator. A subgroup of patients with initial lytic therapy followed by balloon angioplasty several days later was not available for comparison. All patients had similar therapy with intravenous nitroglycerin and heparin. Of the 19 patients, 14 had thrombolytic therapy with or without associated coronary angioplasty and 5 had coronary angioplasty alone.

The interval from onset of symptoms to clinical or angiographic evidence of coronary reperfusion ranged from 2.5 to 4.5 hours (mean 3.7 ± 0.5). This interval in the 14 patients with thrombolytic therapy (with or without angioplasty) (2.5 to 4.5 hours, mean 3.7 ± 0.5) was similar to that in the 5 patients treated with angioplasty alone (3.0 to 4.5 hours, mean 3.8 ± 0.5). The interval from onset of symptoms to death ranged from 0.3 to 11 days (mean 2.9 ± 3). This interval was shorter in the patients with thrombolytic therapy (with or without angioplasty) (0.6 to 4.1 days, mean 2.1 ± 1) than in the patients with angioplasty alone (0.3 to 11 days, mean 5.1 ± 5). The mode of death was progressive congestive heart failure due to underlying acute myocardial infarction (10 patients), sudden ventricular fibrillation (unrelated to acute reperfusion ven-

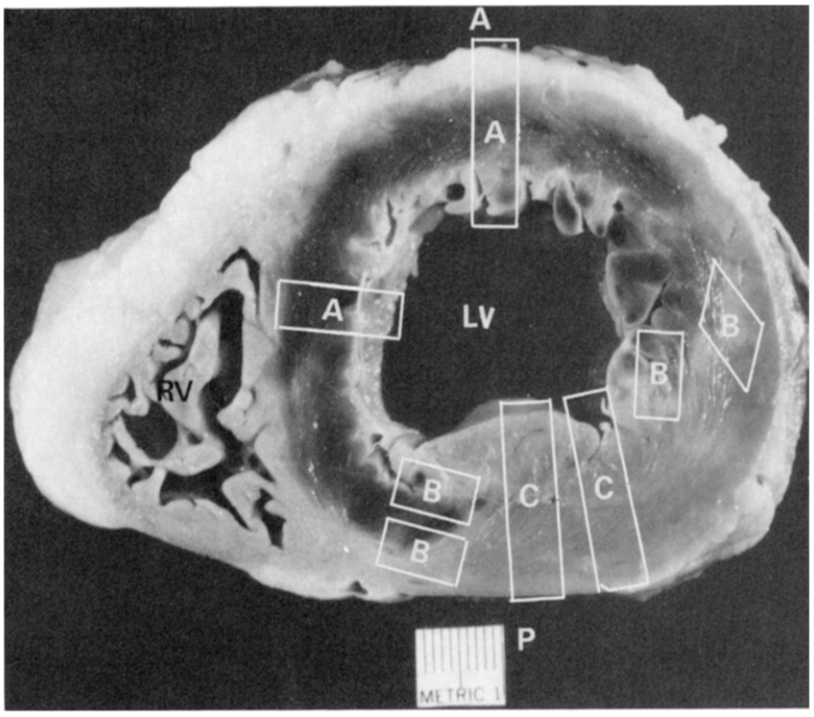


**Figure 1.** Transverse section of ventricular myocardium showing eight sites of histologic sectioning used in the study: A = central zone of necrosis (two areas); B = transition (borderline) zone from necrotic to ischemic to normal myocardium (four areas); C = noninfarcted, nontransition zone myocardium (two areas). A (at top of figure) = anterior; LV = left ventricular cavity; P = posterior; RV = right ventricular cavity.

tricular arrhythmias) (5 patients), left ventricular free wall rupture (2 patients), coronary artery rupture (associated with balloon angioplasty) (1 patient) and noncardiac death (renal failure) (1 patient).

**Necropsy data (Table 1).** All 19 patients had transmural acute myocardial infarction confirmed histologically: 18 patients with coagulative and contraction band necrosis and 1 patient with contraction band necrosis and fiber hypereosinophila. The latter patient died 6 hours after onset of symptoms of acute myocardial infarction (2 hours after acute balloon angioplasty reperfusion). Interstitial necrosis (including necrosis of vascular channel walls) determined histologically was present in the central necrotic zone in 17 patients; it was extensive in 14 of the 17 patients and focal in the remaining 3. Residual (occlusive and nonocclusive) thrombus was found in 16 of the 19 infarct-related coronary arteries; severe underlying atherosclerotic plaque was present in each of these infarct-related arteries.

**Gross myocardial morphology (Table 1).** Of the 19 patients, 14 (74%) had a *hemorrhagic myocardial infarct* (Fig. 2 to 4) and 5 (26%) had an *anemic infarct* (Fig. 5). Hemorrhagic infarction was present in the heart of all 14 patients who were treated with thrombolytic therapy (streptokinase in 13 [Fig. 2 and 3] and tissue-type plasminogen activator in 1 [Fig. 4]) irrespective of associated balloon angioplasty or attempted guide wire perforation of thrombus. No morphologic difference was apparent in hemorrhagic infarcts associated with selective (intracoronary) or systemic (intravenous) streptokinase administration. In marked contrast, all of the five anemic infarcts were present in the heart of patients who received purely mechanical reperfusion therapy (coronary balloon angioplasty) (Fig. 5).

*Among the 14 hearts with hemorrhagic infarction,* 1 heart had only traces of myocardial hemorrhage suggesting temporary or partial reperfusion, or both (Table 1). During systemic streptokinase administration, the patient had a transient decrease in chest pain and ST segment elevation but subsequent fatal sudden ventricular fibrillation 72 hours later. At necropsy, the infarct-related right coronary artery was occluded by severe atherosclerotic plaque and residual thrombus supporting the myocardial observation of limited hemorrhagic necrosis from temporary and partial reperfusion. Among patients with streptokinase therapy, hemorrhagic infarcts were grossly and histologically similar in the nine patients who received streptokinase only (Fig. 2), the three patients with combined streptokinase and balloon angioplasty (Fig. 3) and the one patient with streptokinase and attempted guide wire perforation of coronary thrombus. The hemorrhagic infarct in the patient receiving recombinant tissue-type plasminogen activator was grossly and histologically similar to the hemorrhagic infarcts observed in the patients receiving streptokinase therapy (Fig. 4).

*Among the 14 patients with hemorrhagic infarction,* no morphologic or histologic difference was apparent in the amount of hemorrhage observed with respect to the interval of time from the onset of symptoms to clinical reperfusion (Table 1). Myocardial infarct hemorrhage in patients with reperfusion by 3.5 hours or less (range 2.5 to 3.5, mean

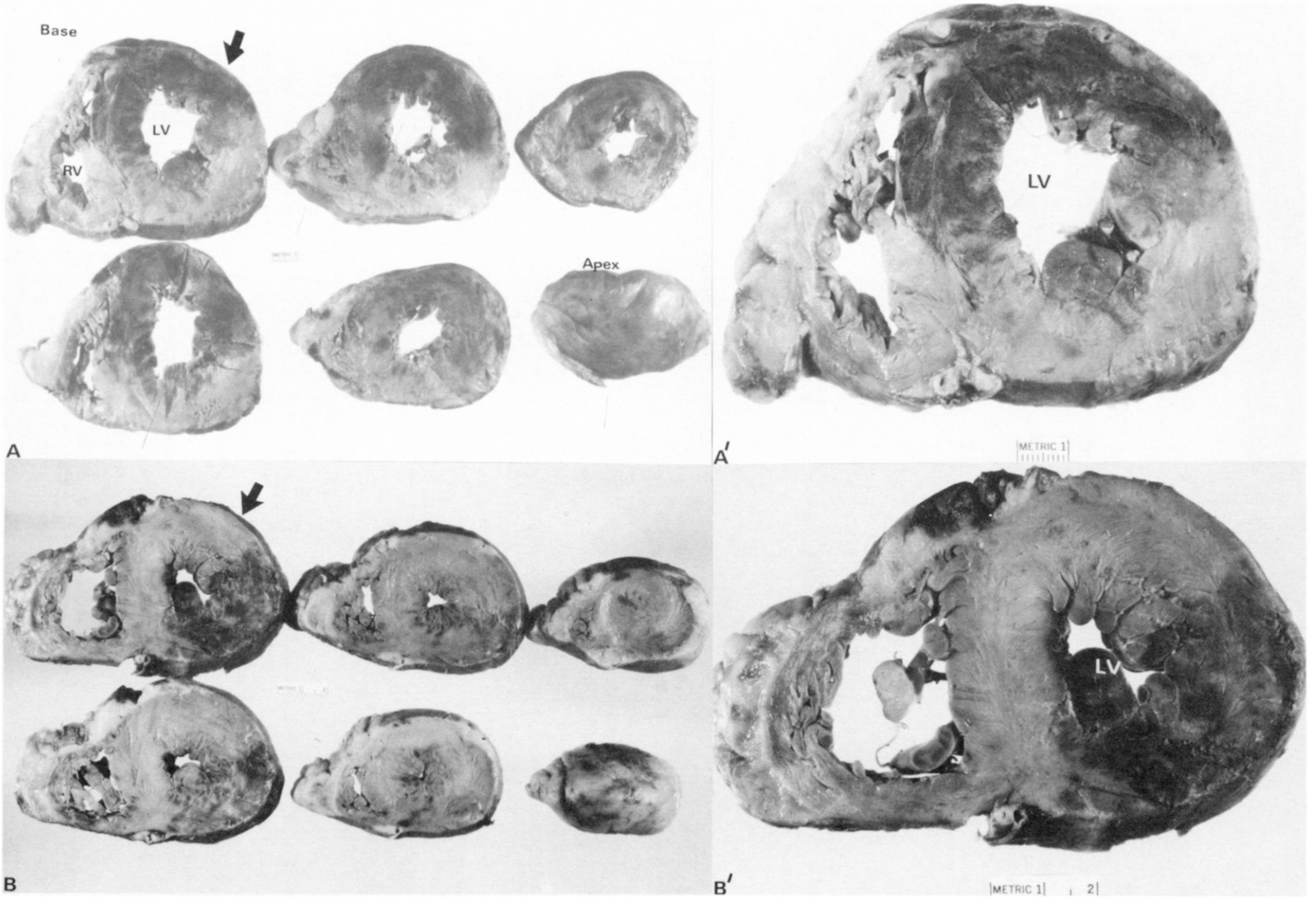


**Figure 2.** Thrombolytic therapy with *streptokinase only*. **A** and **B,** Transverse ventricular slices from the heart of two patients undergoing acute reperfusion therapy with streptokinase infusion (**A** = intracoronary, **B** = intravenous) showing extensive (base to apex), transmural, hemorrhagic myocardial infarction. **Arrows** indicate the respective ventricular slice shown in **A′** and **B′.** Abbreviations as in Figure 1.

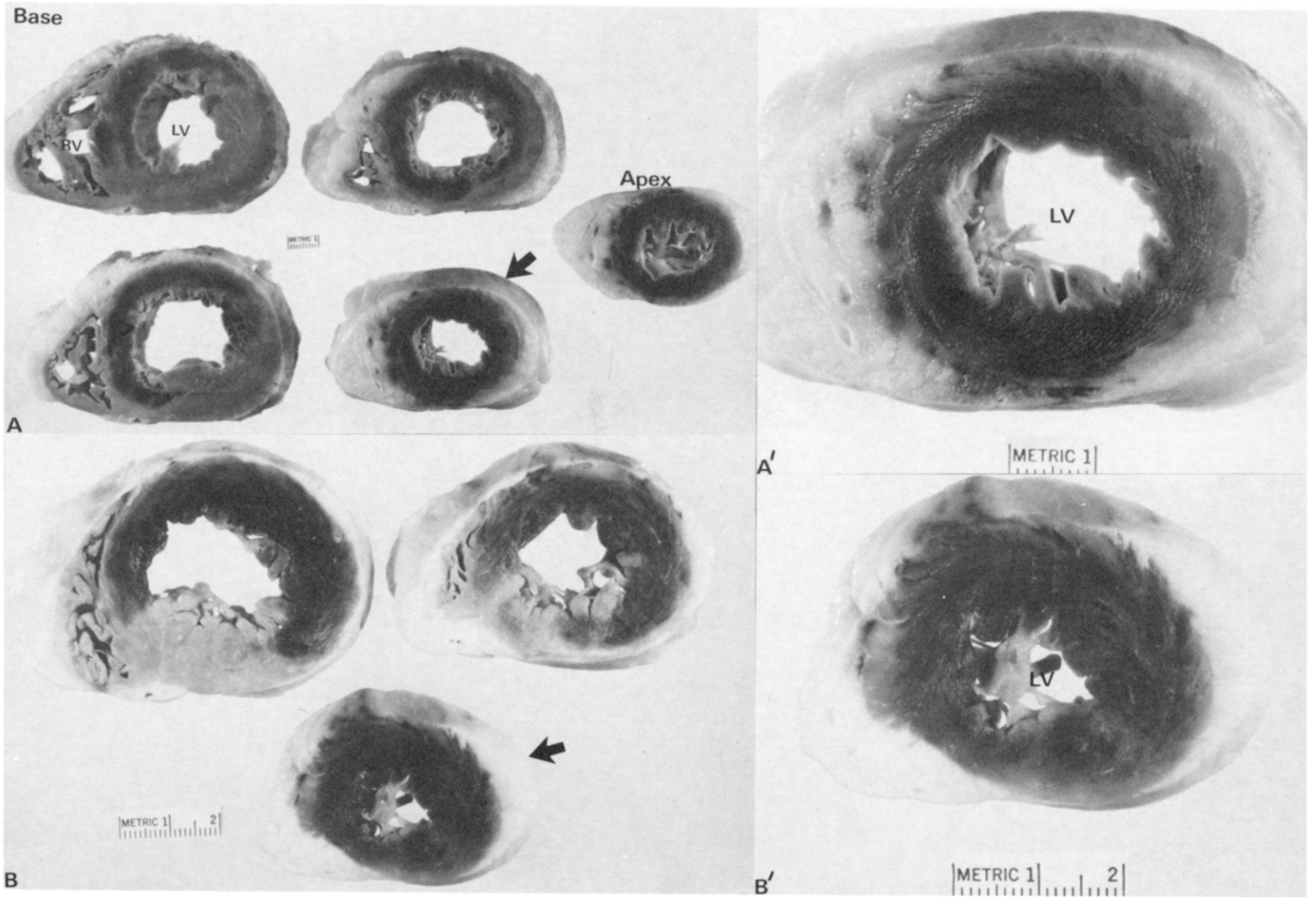


**Figure 3.** Reperfusion therapy using *combined streptokinase and coronary angioplasty*. **A** and **B,** Ventricular slices from the heart of two patients receiving combined reperfusion therapy showing extensive (base to apex), transmural, hemorrhagic myocardial infarction. **Arrows** indicate respective ventricular slices shown in **A′** and **B′.** Compare these findings with findings after the use of streptokinase alone (Fig. 2) and the use of balloon angioplasty alone (Fig. 5). Abbreviations as in Figure 1.

3.3 ± 0.4) was qualitatively similar in extent and severity to myocardial hemorrhage in patients with reperfusion of 3.6 hours or longer (range 4.0 to 4.5, mean 4.2 ± 0.3).

**Myocardial histology.** Histologic sections from the central infarct zones (Fig. 1) showed coagulative necrosis involving myofibers and interstitial vessels. In the 14 hearts with hemorrhagic infarction, the interstitial space was packed with extravasated erythrocytes (Fig. 6A,B,C). In contrast, histologic sections from central infarct zones of three of the five hearts with anemic infarcts disclosed scattered foci of erythrocytes (Fig. 6D). Histologic sections from borderline (transition) zones (Fig. 1) showed extravasated erythrocytes confined to the zone of coagulative necrosis in 10 of the 14 hearts with hemorrhagic infarction, whereas in the remaining four hearts, interstitial spaces between histologically normal-appearing myocytes contained extensive amounts of extravasated erythrocytes which surrounded vascular channels whose walls appeared viable (that is, absent wall necrosis) (Fig. 7A and B).

All four patients with extravasated erythrocytes *outside the zone of necrosis* received intracoronary streptokinase thrombolytic therapy. The interval from onset of symptoms to clinical reperfusion ranged from 3.0 to 4.0 hours (mean 3.5 ± 0.4) and the interval from onset of symptoms to death ranged from 1.0 to 4.1 days (mean 2.4 ± 1). These values did not significantly differ from those of the remaining patients who received streptokinase thrombolytic therapy (2.5 to 4.5 hours, mean 3.7 ± 0.6; 0.9 to 4.0 days, mean 2.0 ± 1, respectively) (Fig. 2, 3, 6 and 7). Histologic sections from the borderline (transition) zones in the anemic infarcts disclosed occasional myocardial contraction bands but the interstitial spaces were free of erythrocytes. Histologic sections of noninfarcted, nontransition zone myocardium (Fig. 1) from all 19 hearts disclosed no extravasated interstitial erythrocytes.

**Residual thrombus in infarct-related coronary artery.** Of the 19 infarct-related coronary arteries, 16 (84%) had residual thrombus at the site of previous occlusion (Fig. 8 and 9). In 9 (56%) of the 16 arteries, the residual thrombus was occlusive (Fig. 9); 6 of the arteries were from patients who had received thrombolytic therapy and 3 were from patients treated only with angioplasty.

**Residual atherosclerotic plaque in infarct-related coronary artery.** The amount of residual atherosclerotic plaque at the site of previous coronary artery occlusion depended on the type of acute reperfusion therapy. All 19 infarct arteries were narrowed greater than 50% in cross-sectional area by atherosclerotic plaque at the site of previous occlusion (Fig. 8 and 9). In 9 (90%) of the 10 patients receiving thrombolytic agents alone, the sites of previous occlusion were narrowed 76 to 100% in cross-sectional area by atherosclerotic plaque. The remaining patient had the site of previous occlusion narrowed 51 to 75% in cross-sectional area. Because of continued pain, this patient was

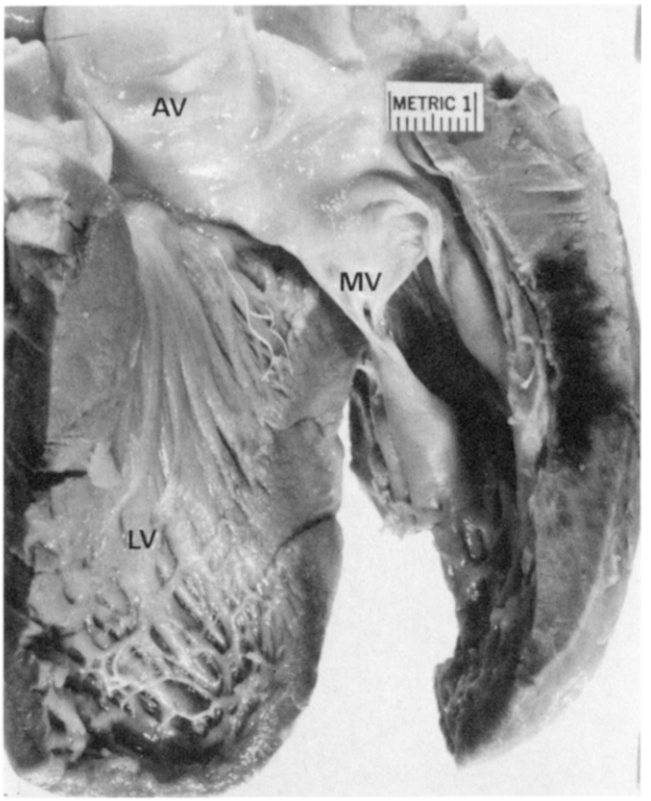


**Figure 4.** Reperfusion therapy with combined *recombinant tissue plasminogen activator and coronary angioplasty.* Transmural, hemorrhagic myocardial infarction is present in the anterior left ventricular (LV) free wall. The patient died after coronary artery rupture. AV = aortic valve; MV = mitral valve.

treated with coronary balloon angioplasty 24 hours after acute intravenous streptokinase therapy. Of the remaining nine patients who had coronary angioplasty (with or without thrombolytic therapy), eight had an infarct artery that was narrowed 51 to 75% in cross-sectional area by plaque (Fig. 9). The remaining patient had an infarct artery narrowed 76 to 100% in cross-sectional area by plaque (Fig. 8). The increased luminal cross-sectional area observed at the site of previous occlusion in the patients treated with balloon angioplasty was due to intimal-medial "cracks" and "breaks" in the atherosclerotic plaque.

**Site of acute angioplasty.** Among the nine patients with acute balloon angioplasty reperfusion therapy, four also received streptokinase (three patients) or tissue-type plasminogen activator (one patient). A major difference between the two subgroups of patients undergoing angioplasty was present at the respective angioplasty sites. External examination of the infarct artery disclosed adventitial *hemorrhage* surrounding the angioplasty site in patients receiving both angioplasty and a thrombolytic agent, but not in those patients treated with angioplasty alone (Fig. 8A). In the four patients with combined angioplasty and thrombolytic therapy, the area of plaque "cracking" also *contained intimal and medial hemorrhage*. Bleeding at the angioplasty site

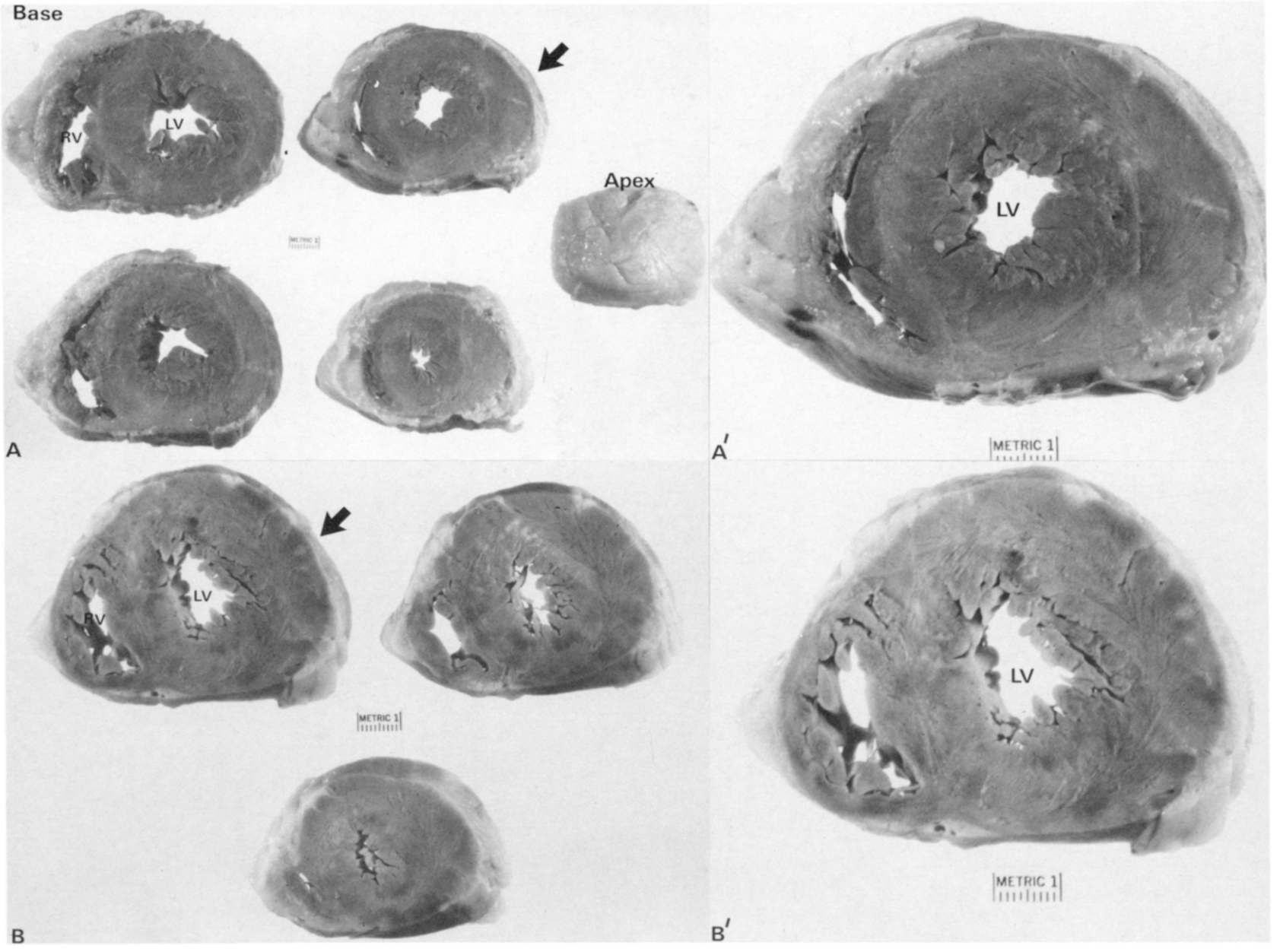


**Figure 5.** Acute reperfusion therapy with *coronary angioplasty alone*. **A** and **B,** Transverse ventricular slices showing no hemorrhagic infarction, from the heart of two patients undergoing purely mechanical reperfusion therapy with balloon angioplasty. **Arrows** indicate respective slices illustrated in **A′** and **B′.** Abbreviations as in Figure 1.

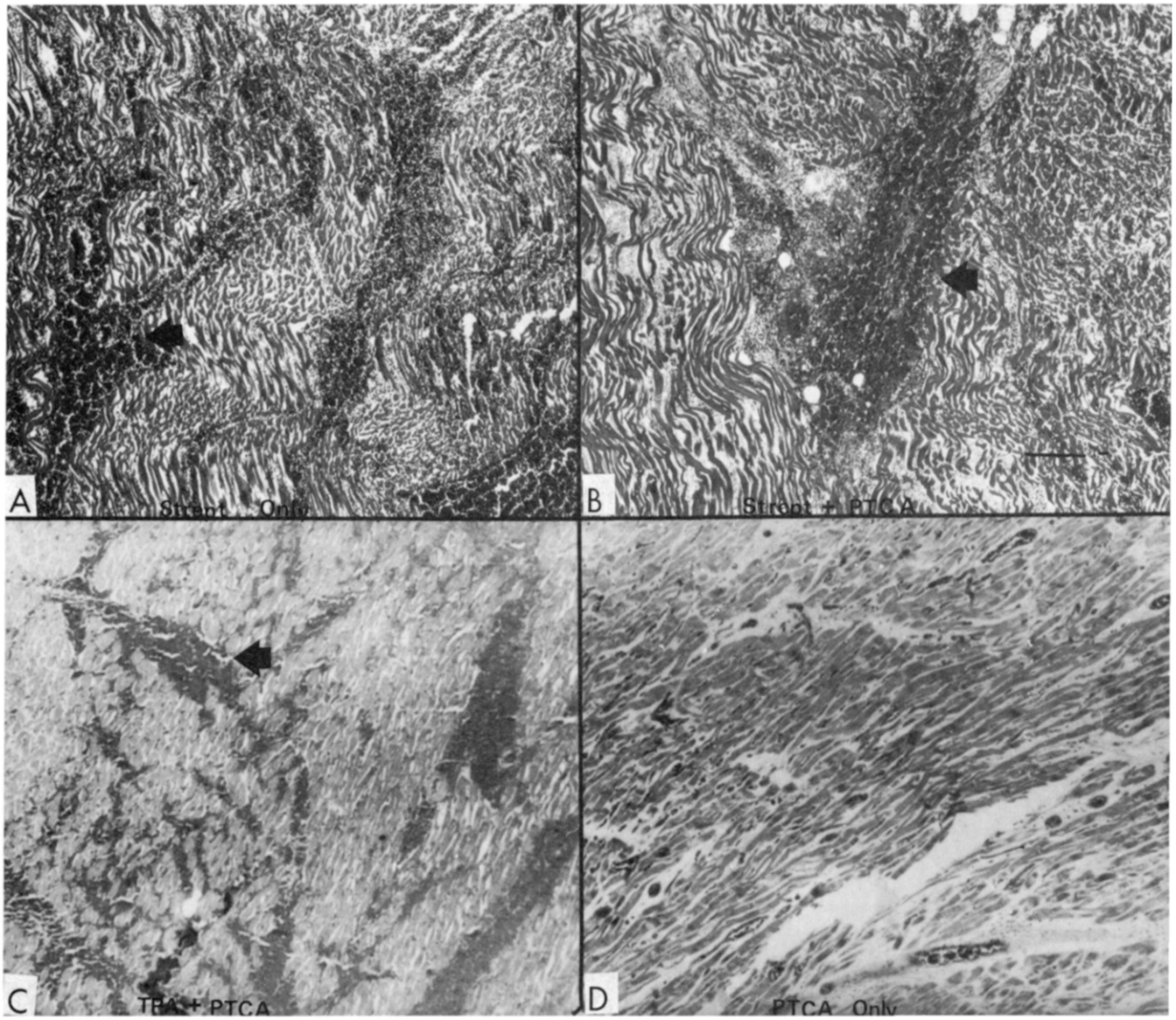


**Figure 6.** Comparison of histologic findings in areas of acute myocardial damage after four types of reperfusion therapy. **A,** Streptokinase (Strept) only, **B,** Streptokinase plus percutaneous transluminal coronary angioplasty (PTCA); **C,** tissue-type plasminogen activator (TPA) plus coronary angioplasty; **D,** angioplasty only. In each type of thrombolytic reperfusion (with or without associated angioplasty), the interstitial space contains massive amounts of extravasated erythrocytes (hemorrhagic infarction) **(arrows),** whereas in the purely mechanical form of reperfusion **(D),** hemorrhagic infarction is absent. Hematoxylin-eosin stains; **A,B,** × 40; **C,** × 10; **D,** × 160; all reduced by 31%.

was severe and compromised the dilated lumen in one patient (Fig. 8B to E). In contrast, the remaining five infarct arteries dilated without the additional use of thrombolytic agents showed intimal-medial "cracks" *without* associated hemorrhagic changes (Fig. 9).

## Discussion

The purpose of this study was to determine the morphologic and histologic status of ventricular myocardium and the infarct-related coronary artery in necropsy patients who had been treated with various types of initially clinically successful reperfusion therapy for evolving acute myocardial infarction. Results of the morphologic and histologic observations permit separation of the patients into distinct subgroups based on changes in the myocardium and infarct coronary artery.

**Myocardium.** Gross and histologic observations in the ventricular myocardium clearly separated the 19 patients into two subgroups: those patients *with* and those *without hemorrhagic myocardial infarction*. Of the 19 necropsy patients, 14 (74%) had a hemorrhagic myocardial infarct and five (26%) had a nonhemorrhagic (grossly anemic) myo-

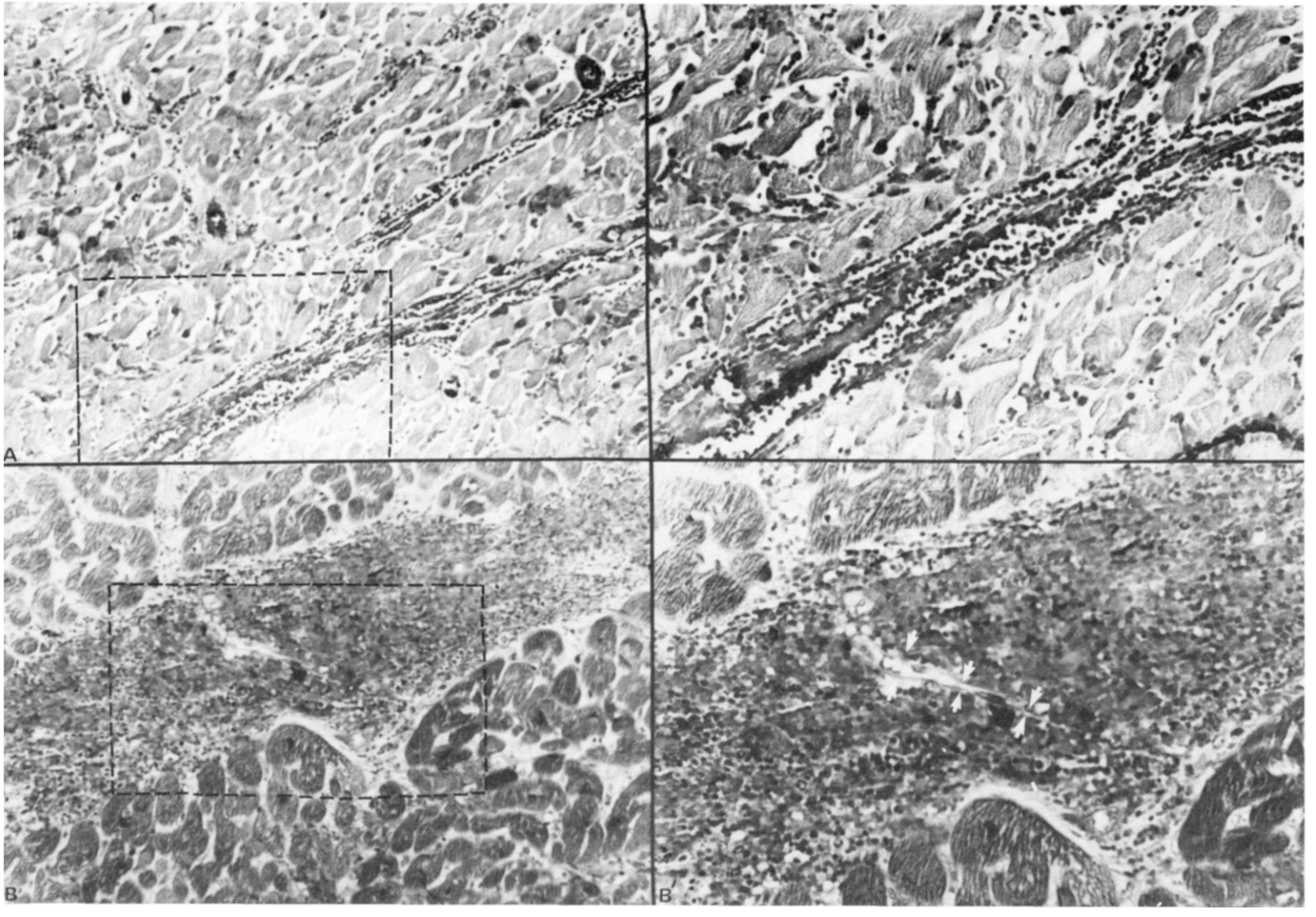


**Figure 7.** Histologic sections near the transition zone of necrotic to viable myocardium from two patients with streptokinase thrombolysis. **A,** Low power ( × 160) view showing interstitial extravasated erythrocytes *outside* the zone of central necrosis. Interstitial hemorrhage is *surrounded* by histologically normal-appearing myocytes. **A′,** Higher magnification ( × 400) of boxed area seen in **A. B,** Photomicrograph from another patient showing massive interstitial hemorrhage outside the zone of myocardial necrosis. A vascular channel within the interstitial space is surrounded by massively extravasated erythrocytes. **B′,** Higher magnification ( × 400) of boxed area in **B** shows potential compression of vascular channels **(arrows)** by erythrocytes packed within the interstitium. Adjacent areas of viable myocardium may be jeopardized because of increased interstitial pressure and subsequent diminished coronary perfusion. This may be a mechanism for infarct expansion in hemorrhagic infarction. All reduced by 31%.

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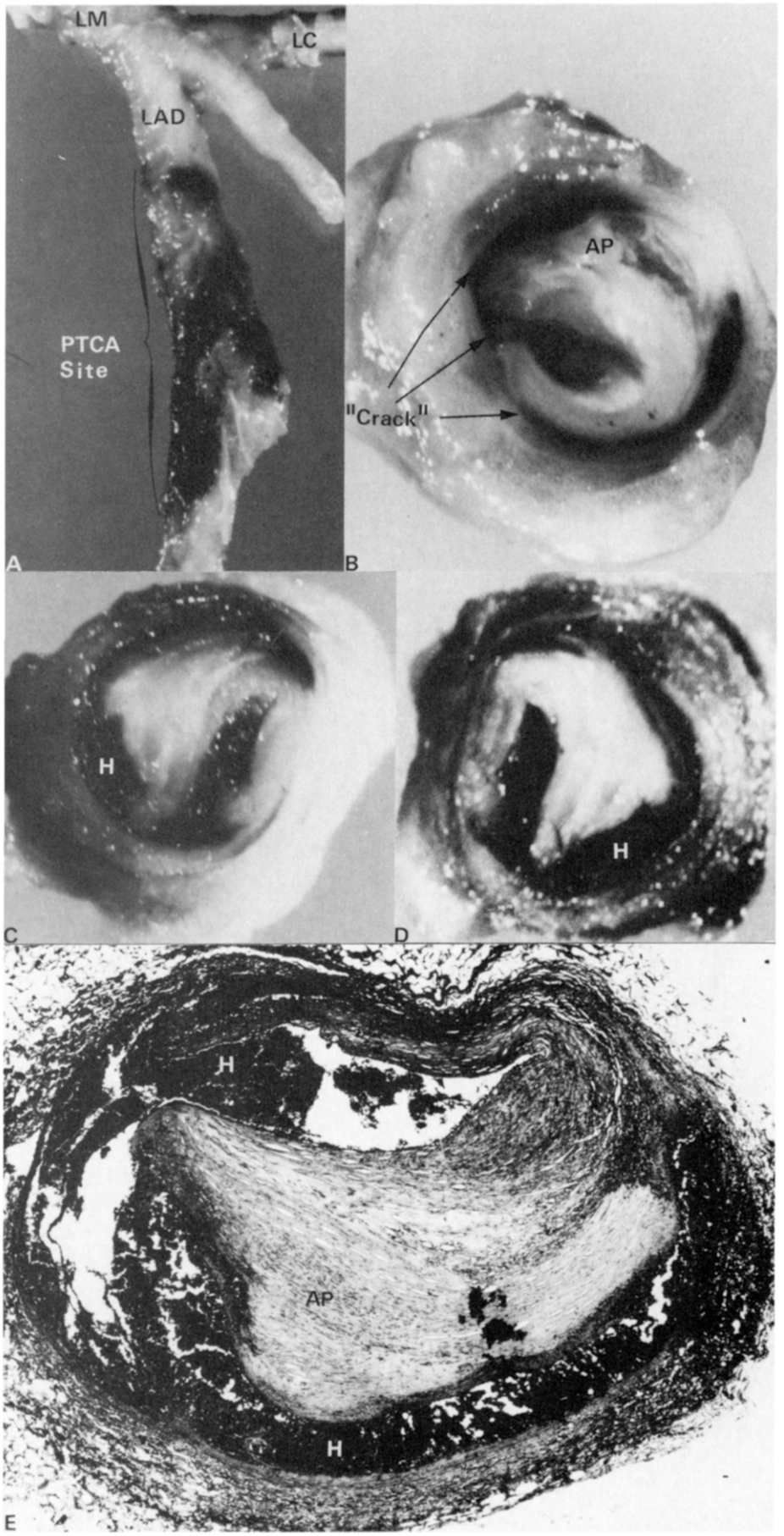


**Figure 8.** Gross and histologic changes in the infarct-related artery (left anterior descending [LAD]) artery of a patient receiving combined streptokinase and coronary angioplasty (PTCA) reperfusion therapy. **A,** External view of the left anterior descending artery discloses severe adventitial hemorrhage surrounding the site of angioplasty. **B, C** and **D,** Transverse coronary sections through the angioplasty site disclose an atherosclerotic plaque (AP) "crack" **(B)** with severe intimal and medial hemorrhage (H). The hemorrhage produces severe coronary luminal narrowing at the site of previous angioplasty luminal expansion **(C** and **D). E,** Histologic section corresponding to the coronary segment illustrated in **D** showing severe medial bleeding (H) (localized dissection) and atherosclerotic plaque (AP) "crack." Similar coronary artery plaque hemorrhage was observed in four patients with *combined angioplasty and thrombolytic therapy* but was absent in infarct-related arteries of patients treated with *angioplasty alone* or *streptokinase alone*.

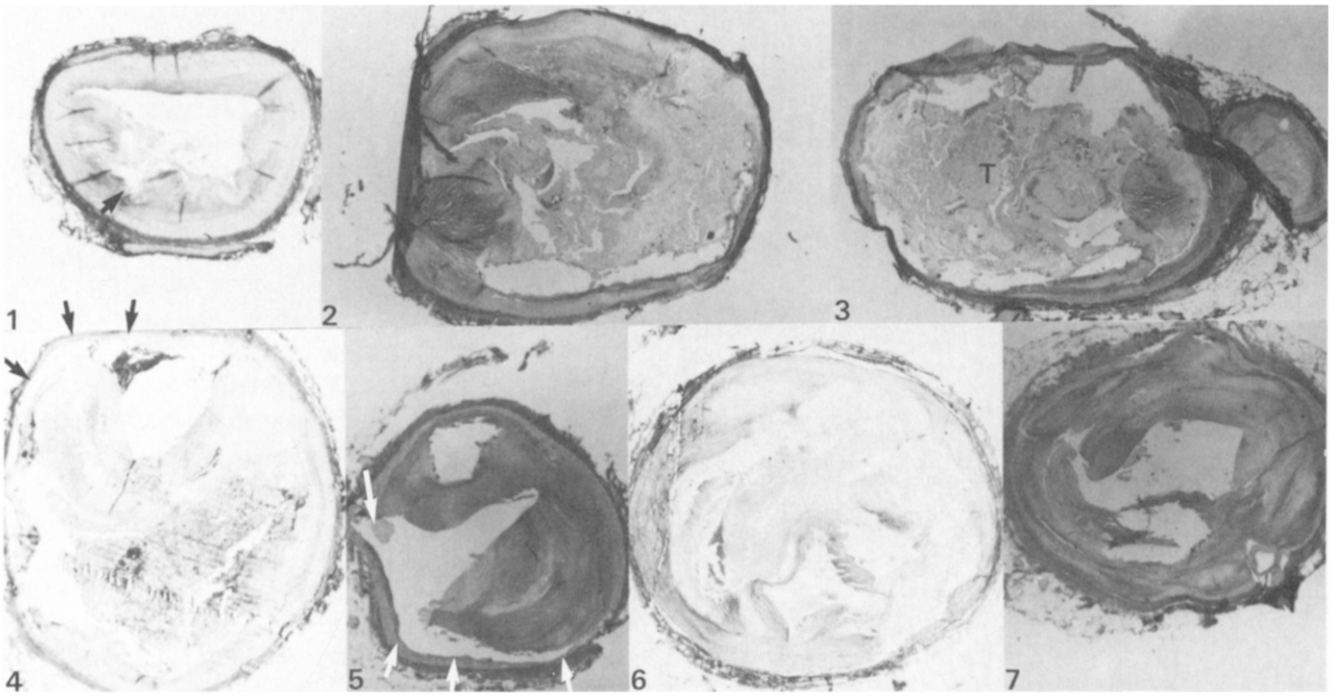


**Figure 9.** Composite of 5 mm histologic cross sections of infarct-related coronary artery (left anterior descending) from a patient with acute reperfusion using coronary balloon angioplasty only. Atherosclerotic plaque "cracks" **(arrows)** expand the coronary lumen (sections **1, 4** and **5**). Occlusive thrombus (T) is present in segments **2** and **3**. Note the absence of intimal, medial and adventitial coronary artery wall hemorrhage in marked contrast to Figure 8 from a patient who underwent combined angioplasty and streptokinase therapy.

cardial infarct. Of the 14 patients with a hemorrhagic infarct, reperfusion therapy consisted of administration of selective (intracoronary) or systemic (intravenous) streptokinase or the use of selective (intracoronary) recombinant tissue-type plasminogen activator. Of these 14 patients with thrombolytic therapy, four also underwent coronary angioplasty as part of the acute reperfusion therapy. Factors such as the use of intracoronary versus intravenous streptokinase infusion, the use of streptokinase versus tissue-type plasminogen activator (although only one patient with tissue-type plasminogen activator was studied) or the use of purely lytic agents versus combined lytic agent plus balloon angioplasty did not alter the occurrence or appearance of the hemorrhagic infarction. In contrast, the remaining five patients with a grossly anemic ventricular infarct received purely mechanical reperfusion therapy with percutaneous balloon angioplasty. *Thus, a common denominator for the patients with hemorrhagic myocardial infarction appears to be related to the lytic effects of the pharmacologic reperfusion agents employed rather than a direct effect of the coronary reperfusion* (Fig. 10).

**Infarct-related artery.** Gross and histologic observations in the infarct-related reperfused coronary artery also separated the 19 necropsy patients into two distinct groups: those patients treated *with* and those *without* coronary angioplasty. Of the 19 necropsy patients, 9 (47%) underwent acute balloon angioplasty and had morphologic evidence of plaque "cracks," "fractures" and medial dissection that appeared to increase the coronary luminal cross-sectional area in eight of the nine arteries dilated. Of the nine dilation sites, eight had a reduction of 51 to 75% in luminal cross-sectional area and one a 76 to 100% narrowing of cross-sectional area by atherosclerotic plaque. In contrast, 9 of the 10 remaining infarct coronary arteries from patients with thrombolytic therapy without balloon angioplasty had no morphologic evidence of plaque disruption or localized medial dissection and the nine sites of previous occlusion were narrowed 76 to 100% in cross-sectional area by atherosclerotic plaque. *Thus, in patients treated with acute angioplasty reperfusion therapy, the sites of previous total occlusion had less luminal cross-sectional area reduction by residual atherosclerotic plaque than did the sites of previous total occlusion in patients treated with thrombolytic agents.*

**Intraplaque hemorrhage in the infarct-related artery.** The nine patients receiving acute angioplasty reperfusion therapy also can be separated into two distinct subgroups: those patients treated with *angioplasty alone* and those treated with *angioplasty and thrombolytic agents*. In the five patients treated with angioplasty alone, the site of angioplasty had plaque "fractures" and "cracks" *without* intimal or medial hemorrhage. In contrast, in the four patients treated with angioplasty plus thrombolytic therapy, the site of angioplasty had plaque "fractures" and "cracks" *with* hemorrhage involving the intimal, medial and adventitial layers

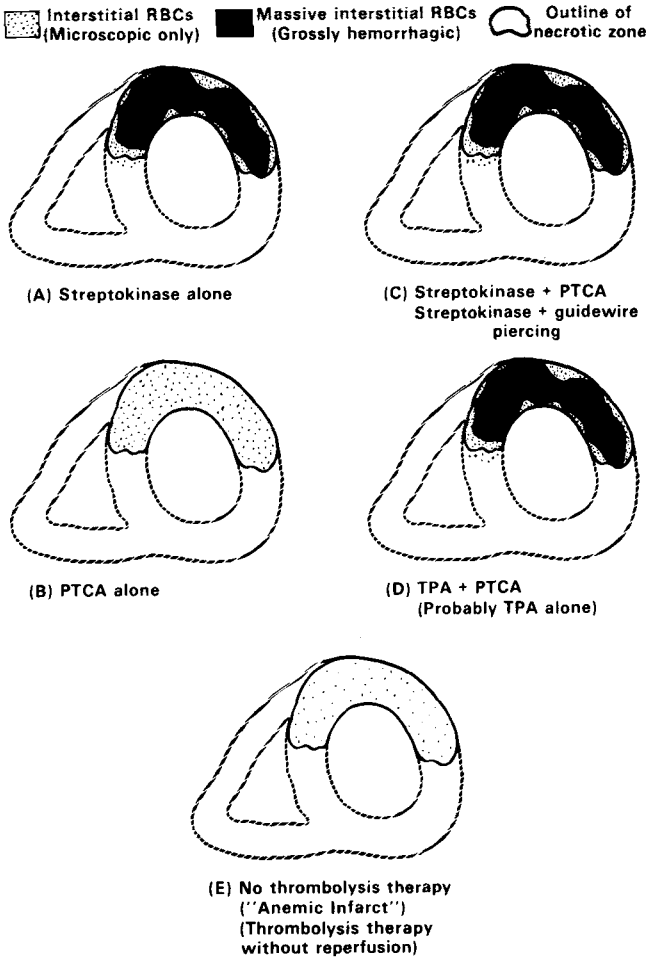


**Figure 10.** Diagram summarizing myocardial interstitial hemorrhage in the present study in evolving acute myocardial infarction after various forms of reperfusion therapy. Massive interstitial hemorrhage (hemorrhagic infarct) was observed in patients with reperfusion using streptokinase alone or in combination with coronary angioplasty (PTCA), and in patients with reperfusion using tissue plasminogen activator (TPA) with angioplasty. Hemorrhagic infarction was absent in patients with angioplasty alone or in myocardial infarction without acute intervention or without reperfusion. Interstitial hemorrhage was not limited to the zone of necrosis. RBCs = red blood cells.

of the coronary artery. In one patient, the hemorrhage was so extensive that it narrowed the coronary lumen at the angioplasty site. In the 10 patients receiving streptokinase therapy alone, intraplaque hemorrhage was absent. *Thus, the use of combined angioplasty and thrombolytic agents in acute reperfusion therapy may produce localized bleeding at the angioplasty site and the bleeding may produce additional coronary luminal narrowing.*

**Previous studies.** Despite the widespread clinical use of various forms of acute reperfusion therapy during evolving acute myocardial infarction, cardiac necropsy observations are limited (1–14). Several studies (15–32) report deaths or causes of death in patients with reperfusion therapy but do not provide necropsy data. In 14 reports with necropsy data (1–14), 100 patients have been described in case reports or as part of larger series. Of these 100 patients, 67 received streptokinase alone, 31 urokinase alone and 2 streptokinase plus percutaneous transluminal angioplasty. Specific information on the two patients with combined pharmacologic and mechanical therapy was not provided (5,6). In nine studies (93 patients) (1–3,6,10–13), information was provided on the status of the myocardium. Hemorrhagic infarction was described in 43 (46%) of these 93 patients. Explanation for the absence of hemorrhage in the remaining hearts was not provided. Fujiwara et al. (13) studied 30 necropsy patients after selective intracoronary thrombolysis with urokinase. Three stages of infarction were described based on the interval of time (hours) after thrombolytic therapy. Hearts of patients in stage II (9 hours to 11 days after thrombolytic therapy) had hemorrhagic infarction (15 of 18 patients). These authors concluded that myocardial hemorrhage increases gradually after acute thrombolytic therapy, becoming moderately or markedly diffuse after 4 hours. They speculated that hemorrhagic infarction is due to the combined effects of reperfusion and large doses of urokinase. Mathey et al. (6) described transmural, hemorrhagic myocardial infarction after intracoronary streptokinase in six patients who died 1 to 18 days after thrombolytic therapy. They suggested that sudden reperfusion after 3 to 4 hours of coronary artery occlusion was a major determinant in the development of myocardial hemorrhage and the hemorrhage probably was not the consequence of streptokinase use as such. Eleven reports (1–4,6–10,12) provide some information on the status of the infarct-related coronary artery: 29 patients had residual coronary thrombus and 47 patients had various degrees of underlying atherosclerotic plaque.

**Hemorrhagic myocardial infarction.** Hemorrhagic myocardial infarction as defined earlier consists of grossly visible myocardial blood that histologically is composed of massive sheets or pools of interstitial erythrocytes. Focal areas of scattered interstitial erythrocytes within an area of myocardial necrosis detected only histologically do not appear to produce the grossly visible hemorrhagic infarct. Hemorrhagic infarcts frequently coincide with reperfusion efforts during an evolving acute myocardial infarction (1–3,6,8,10–13) or during aortocoronary bypass grafting (33,34), whereas myocardial hemorrhage in acute myocardial infarction without intervening thrombolysis or revascularization therapy is distinctly unusual. In a study (35) of 119 necropsy patients with fatal acute myocardial infarction without the preceding interventions, 3 (2%) had hemorrhagic infarction. In one of these three patients, overwhelming sepsis with disseminated intravascular coagulation developed surrounding the acute infarct during repair of an abdominal aortic aneurysm. The coagulation abnormality may have provided a "natural" thrombolytic state similar to the pharmacologically induced thrombolytic state

of reperfusion therapy. Reasons for the other two hemorrhagic infarcts are unknown. Mathey et al. (6) found hemorrhagic infarction in none of 200 necropsy patients with fatal acute myocardial infarction without interventional therapy. Of 60 necropsy patients with acute myocardial infarction without thrombolytic therapy studied by Fujiwara et al. (13), 2 (3%) had "moderate diffuse hemorrhage" (hemorrhagic infarction).

To our knowledge, only two patients have been described in whom the clinical diagnosis of hemorrhagic infarction was made after acute thrombolytic therapy (11,36). Little and Rogers (36) reported angiographic evidence of intramyocardial contrast pooling (representing interstitial extravasation of erythrocytes) after successful streptokinase therapy. The patient's condition subsequently deteriorated with infarct extension. Necropsy documentation of hemorrhagic infarction was not provided. Yasuno et al. (11) reported on an 83 year old man with angiographic findings suggestive of intramyocardial hemorrhage after urokinase treatment. At necropsy, marked transmural hemorrhagic necrosis was observed in the corresponding area. Yasuno et al. (11) suggested stopping thrombolytic agent administration if angiographic evidence of hemorrhagic infarction is observed.

Debate continues as to whether the presence of hemorrhage within zones of necrosis delays (6) or accelerates (37) healing of infarcted myocardium or whether it expands or accelerates myocardial necrosis (38). Mathey et al. (6) described a patient with two infarcts of equal age in whom one infarct-related artery was reperfused and the other not; at necropsy, the reperfused artery was associated with a hemorrhagic infarct and the nonreperfused artery with an anemic infarct. Distinct histologic differences were noted between the hemorrhagic and anemic infarcts in terms of removal of necrotic tissue and replacement by connective tissue. The hemorrhagic infarct had no evidence of repair after 18 days, whereas the anemic infarct showed typical resorption and repair by granulation tissue. This difference indicated a marked delay in the usual infarct healing process in the hemorrhagic infarct (6).

**Experimental results and clinical differences.** Experimental studies in various animals (rats, dogs, pigs) have been performed to define potential benefits and hazards of acute myocardial reperfusion. Results of these studies have been divergent in areas of hemorrhagic infarction, infarct size reduction or expansion, wall motion changes and altered survival. Some investigators (37,39–47) found hemorrhagic infarction in experimental animals confined to areas of necrosis sparing the subepicardial zone (that is, "subendocardial infarction") and found no evidence of infarct expansion. Other investigators (38,48–50) suggested that the myocardial hemorrhage is not strictly confined to the necrotic zone and that infarct expansion may occur with interstitial hemorrhage. The application of experimental reperfusion studies to humans has its limitations with regard to the animal model used, the nature of coronary artery occlusion (coronary ligation versus occlusion by atherosclerotic plaque and thrombus), the presence or absence of collateral circulation and the rate of the occlusion process (slow versus fast). As a consequence of these limitations, at least two major differences exist between hemorrhagic myocardial infarcts observed in necropsy patients and in those observed in experimental animals. First, in patients the hemorrhagic infarction is *transmural* and not subendocardial as has been described in experimental models (51). Second, *extension of the hemorrhage into areas of noninfarcted myocardium* has been observed in previously reported necropsy patients (13) as well as in our present study and may not be confined to the central necrotic zone as has been described in most experimental models (40,43,45,51) (Fig. 10).

**Clinical-pathologic correlation of the effects of myocardial reperfusion.** Significant improvement in left ventricular function after acute coronary reperfusion with streptokinase was not observed in several controlled trials of intracoronary or intravenous streptokinase therapy (14,17,19,21,52). Only one controlled study (18) using intracoronary streptokinase in acute myocardial infarcion showed improvement in serially assessed left ventricular ejection fraction. In contrast, a recently controlled trial (53) comparing intracoronary streptokinase and coronary angioplasty during evolving acute myocardial infarction showed that left ventricular ejection fraction significantly improved during serial testing in the angioplasty group but not in the streptokinase-treated group. In addition, these authors (53) noted that residual luminal stenosis in the infarct-related artery was significantly decreased angiographically after angioplasty as compared with after streptokinase therapy. O'Neill et al. (53) suggested that acute angioplasty is significantly more effective than streptokinase infusion in alleviating the underlying coronary stenosis and that this factor may result in more effective preservation of left ventricular function after acute reperfusion therapy.

The morphologic and histologic findings in the infarct-related coronary artery in our study support these angiographic observations of increased luminal cross-sectional area after angioplasty reperfusion compared with thrombolytic reperfusion therapy. The striking difference between hemorrhagic infarcts present in our thrombolytic group compared with the anemic infarcts in our pure angioplasty group suggests that myocardial hemorrhage also may be a factor in the lack of clinical improvement in left ventricular function in the streptokinase-treated patients. However, additional factors such as the time interval between onset of myocardial infarction and clinical reperfusion, the presence of collateral circulation and the altered contractility of noninfarcted myocardium in the acute and follow-up state may contribute to the lack of improvement in ejection fraction after thrombolytic therapy.

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